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(54) Title: ENHANCED INDOLINONE BASED PROTEIN KINASE INHIBITORS

(57) Abstract: Alpha-hydroxy- omega-(2-oxo-indolylidenemethyl-pyrrole-3'-carbonyl) amino alkanoic acid and amide derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.

ENHANCED INDOLINONE BASED PROTEIN KINASE INHIBITORS

Description

Field of Invention:

The invention relates to protein kinase inhibitors and to their use in treating disorders related to abnormal protein kinase activities such as cancer and inflammation. More particularly, the invention relates to alpha-hydroxy-ω-(2-oxo-indolylidenemethyl-pyrrole-3'-carbonyl) amino alkanoic acid and amide derivatives and their pharmaceutically acceptable salts employable as protein kinase inhibitors.

Background:

Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, considerable effort has been directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules that act as protein kinase inhibitors.

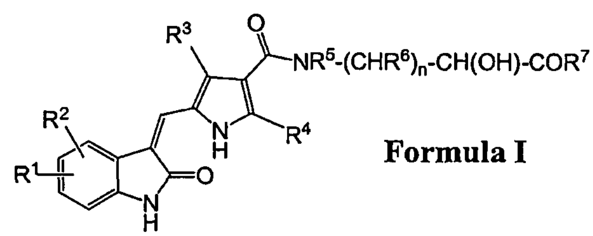
Several pyrrolyl-indolinone derivatives have demonstrated excellent activity as inhibitors of protein kinases (Larid et al. FASEB J. 16, 681, 2002; Smolich et al. Blood, 97, 1413, 2001; Mendel et al. Clinical Cancer Res. 9, 327, 2003; Sun et al. J. Med. Chem. 46, 1116, 2003). The clinical utility of these compounds has been promising, but has been partially compromised due to the relatively poor aqueous solubility and/or other drug properties.

What is needed is a class of modified pyrrolyl-indolinone derivatives having both inhibitory activity and enhanced drug properties.

Summary:

The invention is directed to alpha-hydroxy- omega-(2-oxo-indolylidenemethyl-pyrrole-3'-carbonyl) amino alkanoic acid and amide derivatives and to their use as inhibitors of protein kinases. It is disclosed herein that alpha-hydroxy- ω-(2-oxo-indolylidenemethyl-pyrrole-3'-carbonyl) amino alkanoic acid and amide derivatives have enhanced and unexpected drug properties that advantageously distinguish this class of compounds over known pyrrolyl-indolinone derivatives having protein kinase inhibition activity and over their corresponding beta-hydroxy- ω-(2-oxo-indolylidenemethyl-pyrrole-3'-carbonyl) amino alkanoic acid and amide derivatives. It is also disclosed herein that alpha-hydroxy- ω-(2-oxo-indolylidenemethyl-pyrrole-3'-carbonyl) amino alkanoic acid and amide derivatives are useful in treating disorders related to abnormal protein kinase activities such as cancer.

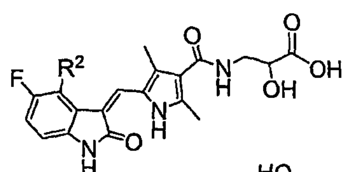
One aspect of the invention is directed to a compound represented by Formula (I):



Formula I

In Formula (I), R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl; R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, (C2-C8) alkoxyalkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino; R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide; R^4, R^5 and R^6 are

independently selected from the group consisting of hydrogen and (C1-C6) alkyl; R^7 is selected from the group consisting of hydroxy, (C1-C6) O-alkyl, (C3-C8) O-cycloalkyl, and NR^8R^9; where R^8 and R^9 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^8 and R^9 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; and **n** is 1, 2, or 3. Alternatively, this aspect of the invention may be directed to a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug of the compound of Formula (**I**). Preferred species of the invention include compounds represented by the following structures: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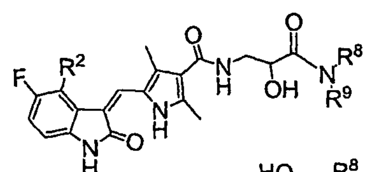
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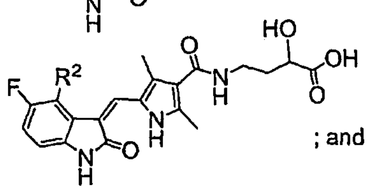
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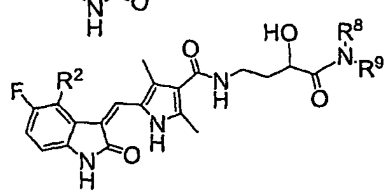
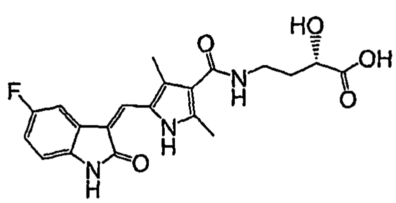


In the above structures, R^2 is selected from the group consisting of hydrogen and fluoro. More particularly, a preferred stereoisomer is represented by the following structure: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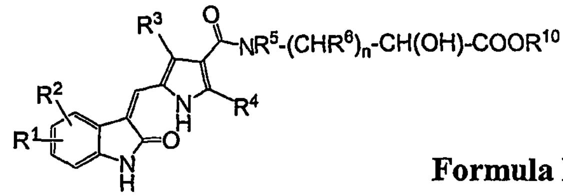
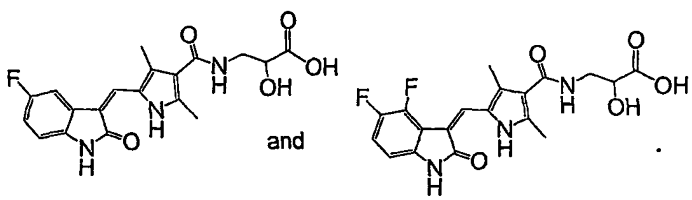
A first subgenus of this aspect of the invention is represented by Formula (**II**):

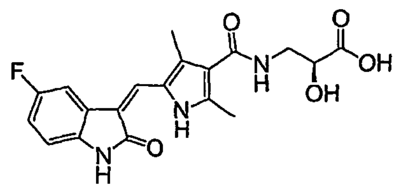


Formula II

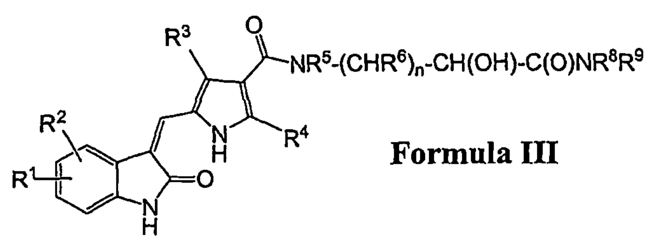
In Formula (**II**), R^{10} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl. In preferred species of this first subgenus, R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro; R^3 and R^4 are methyl; R^5, R^6, and R^{10} are hydrogen; and **n** is 1 or 2. Preferred species are represented by the following compounds:



A preferred chiral species is represented by the following compound:



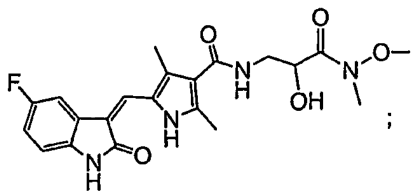
A second subgenus of this aspect of the invention is directed to a compound according to Formula (**III**) or a salt, tautomer, or prodrug thereof:



Formula III

In preferred species of this second subgenus, R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, cyano; R^3, R^4, R^5 and R^6 are independently hydrogen or (C1-C6))alkyl; **n** is 1 or 2; and R^8 and R^9 are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid,

(C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^8 and R^9 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids. Preferred species of the second subgenus are represented by the following structures: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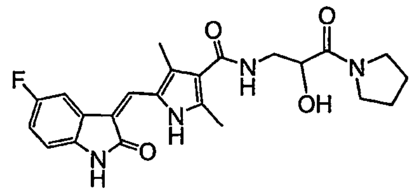
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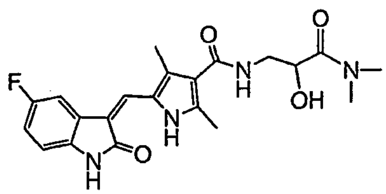
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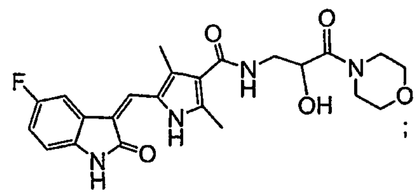
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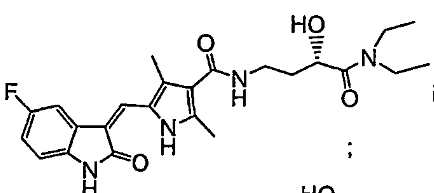
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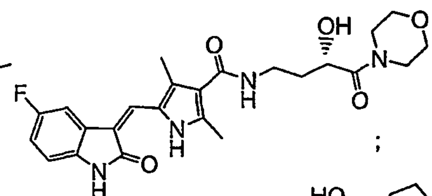
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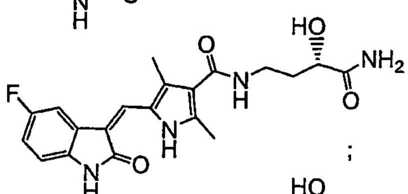
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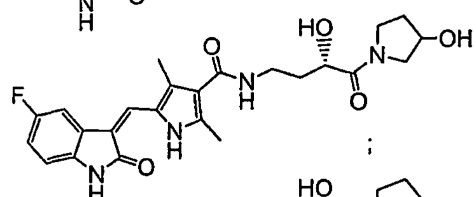
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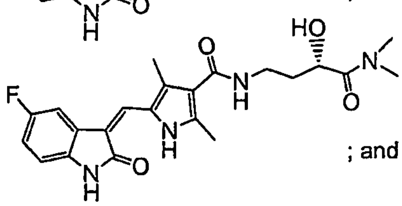
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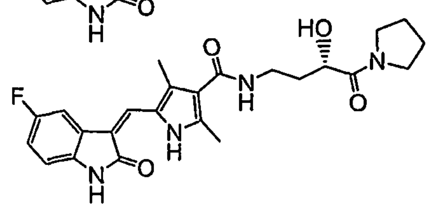
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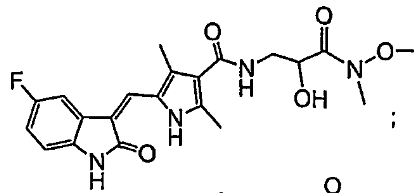
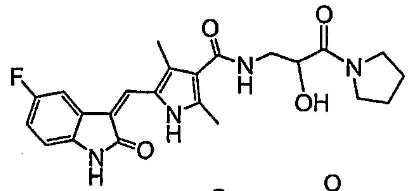
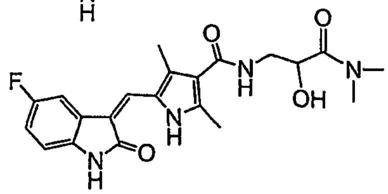
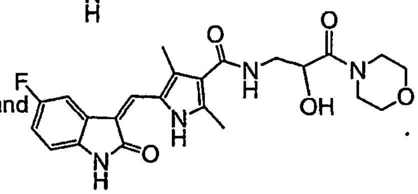
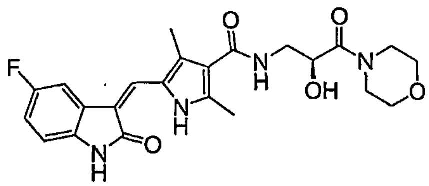
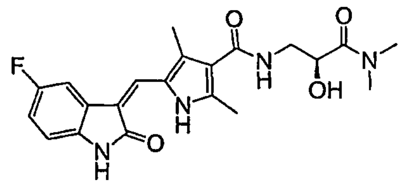
In a first subset of the second subgenus, **n** is 1. Preferred species within this first subset are represented by the following structures:

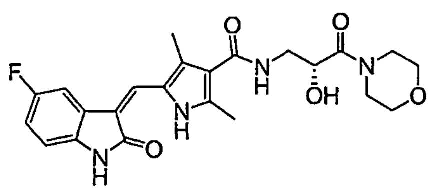
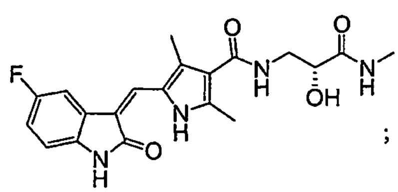
 ;  ;

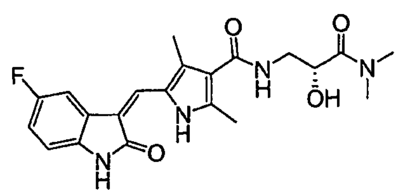
 ; and  .

Preferred chiral species within the first subset of the second subgenus are represented by the following structures:

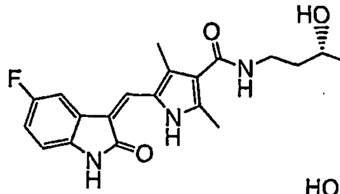
 ;  .

Further preferred chiral species within the first subset of the second subgenus are represented by the following structures:

 ;  ;

 .

In a second subset of the second subgenus, **n** is 2. Preferred species within this first subset are represented by the following structures: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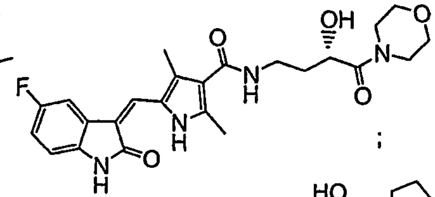
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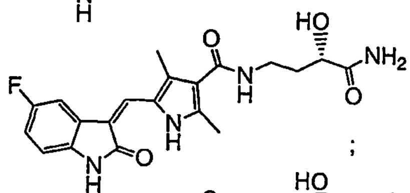
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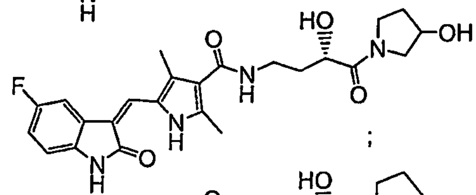
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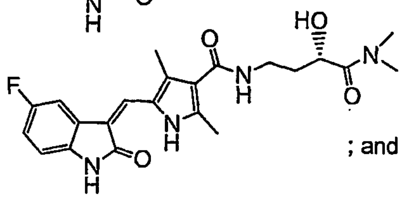
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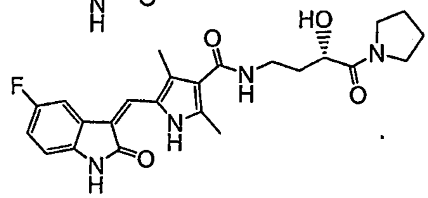
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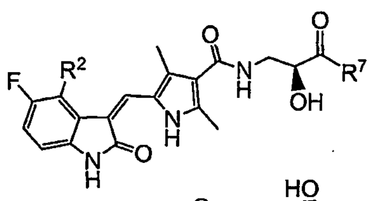
Further preferred species of the first aspect of the invention are represented by the following structures: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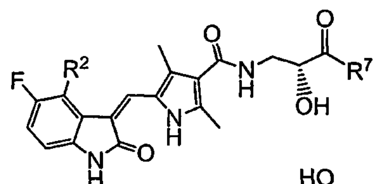
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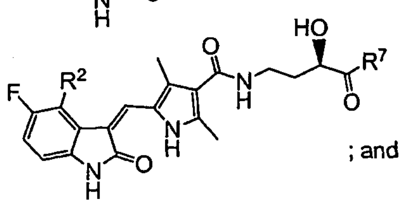
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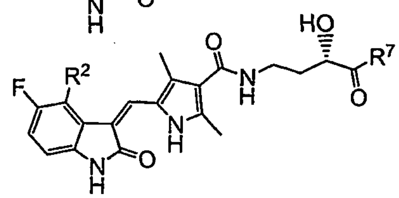
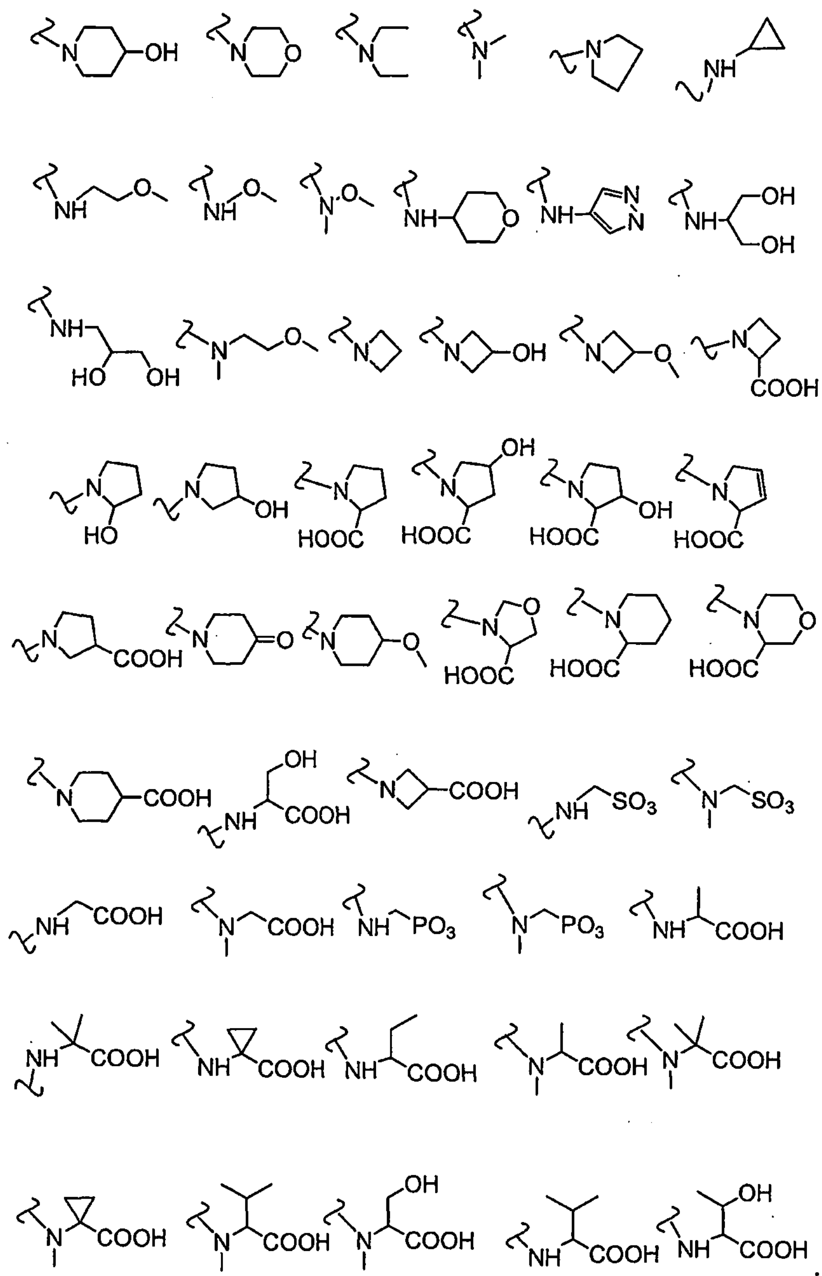


In the above structures, R^2 is selected from the group consisting of hydrogen and fluoro; and R^7 is selected from the group consisting of hydroxyl or radicals represented by the following structures:



A second aspect of the invention is directed to a method for the modulation of the catalytic activity of a protein kinase with a compound or salt represented by Formulas **I-III**, above. In a preferred mode of the second aspect of the invention, said protein kinase is selected from the group of receptors consisting of VEGF, PDGF, c-kit, Flt-3, Axl, and TrkA.

Utility:

The present invention provides compounds capable of regulating and/or modulating protein kinase activities of, but not limited to, VEGFR and/or PDGFR. Thus, the present invention provides a therapeutic approach to the treatment of disorders related to the abnormal functioning of these kinases. Such disorders include, but not limited to, solid tumors such as glioblastoma, melanoma, and Kaposi's sarcoma, and ovarian, lung, prostate, pancreatic, colon and epidermoid carcinoma. In addition, VEGFR/PDGFR inhibitors may also be used in the treatment of restenosis and diabetic retinopathy.

Furthermore, this invention relates to the inhibition of vasculogenesis and angiogenesis by receptor-mediated pathways, including the pathways comprising VEGF receptors, and/or PDGF receptors. Thus the present invention provides therapeutic approaches to the treatment of cancer and other diseases which involve the uncontrolled formation of blood vessels.

Brief Description of Drawings:

Figure 1 illustrates a scheme showing the synthesis of the acid **1-3** and the corresponding amides, **1-4**. The starting carboxylic acid is synthesized according to the supplemental material of Sun, L.; et al., *J. Med. Chem.* **2003**, *46*, 1116-1119.

Figure 2 illustrates a scheme showing the synthesis of the amide series, **2-3**.

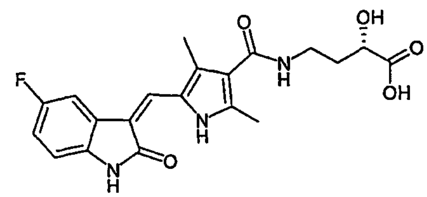
Figure 3 shows example compounds and some of their activities against KDR.

Figure 4 shows additional compounds that were tested for activity.

EXAMPLES

<u>Examples 1-7</u>: The synthesis of acid (**1-3**) and amides (**1-4**) is shown in Figure 1.

Example 1: (*S*)-4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxy-butyric acid:

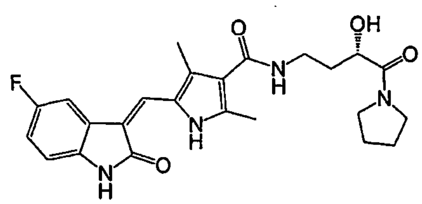


Compound **1-1** was prepared by following a literature procedure used for similar compounds (Li Sun, Chris Liang, et al; Discovery of 5-[5-Fluoro-2-oxo-1,2-dihydroindol-(3*Z*)-ylidenemethyl]-2,4- dimethyl-1*H*-pyrrole-3-carboxylic Acid (2-Diethylaminoethyl)amide, a Novel Tyrosine Kinase Inhibitor Targeting Vascular Endothelial and Platelet-Derived Growth Factor Receptor Tyrosine Kinase. *J. Med. Chem.* **2003**, *46*, 1116 – 1119). Compound **1-1** and DIEA (di-isopropyl ethylamine) (3 equiv) were suspended in dry DMF at room temperature (Figure 1). After sonication (5 min), HATU (0.99 equiv) was added. The suspension became a clear solution after stirring approximately 1 minute at room temperature. Precipitation was observed after another 15 min. After DMF was removed under reduced pressure, anhydrous acetonitrile was added. The precipitate was collected by filtration, washed several times using acetonitrile, and dried under high vacuum for 2 days to give compound **1-2**. LC-MS and NMR spectroscopy confirmed the structure of **1-2**. To a solution of compound **1-2** (1.27 mmol) and DIEA (3 equiv) in DMF, the hydrogen chloride salt of methyl (2S)-4-amino-2-hydroxybutyrate (1.5 equiv, prepared earlier by refluxing the free amino acid (Aldrich) in dry methanol with 1.2 equiv HCl) was added. After stirring at 25 °C for 2h (at which time LC-MS showed the completion of the reaction), KOH in water (5 equiv) was added, and stirring was continued until the hydrolysis was complete (monitored by LC-MS). The solvents were removed by evaporation under reduced pressure. Aqueous HCl (1N) was added to the residue, and the precipitate was collected by filtration, washed with water, and dried under high vacuum to

obtain the title compound (0.5g, 98%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{20}H_{20}FN_3O_5$: 402, obtained: 402.

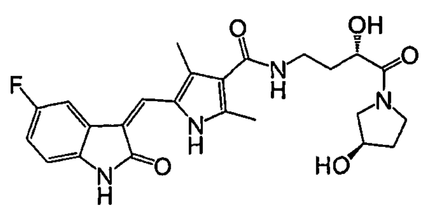
Example 2-7: The general procedure for the synthesis of amides of **Example 1:** An amine (2 equiv) was added to a solution of the acid from **Example 1**, HATU (1.05 mmol), and DIEA (5 equiv) in DMF (5 mL). After the solution was stirred at 25 °C for 2h, aqueous HCl (2 mL, 1N) was added. This solution was subjected to preparative HPLC to obtain the pure amide product, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 2: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1 H-pyrrole-3-carboxylic acid ((S)-3-hydroxy-4-oxo-4-pyrrolidin-1-yl-butyl)-amide



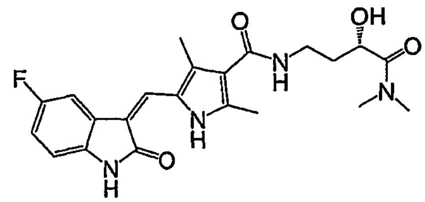
Preparative HPLC gave 32 mg of the title compound (34%) from 90 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{27}FN_4O_4$: 455, obtained: 455.

Example 3: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1 H-pyrrole-3-carboxylic acid [(S)-3-hydroxy-4-((R)-3-hydroxy-pyrrolidin-1-yl)-4-oxo-butyl]-amide



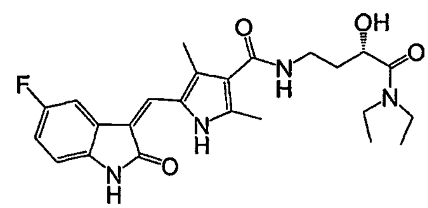
Preparative HPLC gave 27 mg of the title compound (41%) from 61 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{27}FN_4O_5$: 471, obtained: 471.

Example 4: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1 H-pyrrole-3-carboxylic acid ((S)-3-dimethylcarbamoyl-3-hydroxy-propyl)-amide



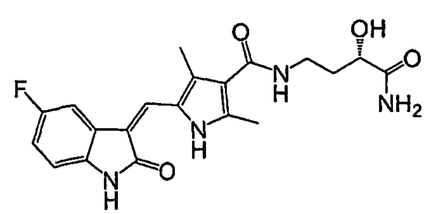
Preparative HPLC gave 22 mg of the title compound (37%) from 61 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{22}H_{25}FN_4O_4$: 429, obtained: 429.

Example 5: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-3-di-ethylcarbamoyl-3-hydroxy-propyl)-amide



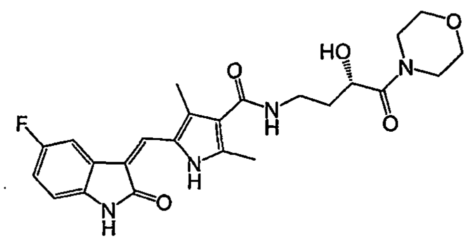
Preparative HPLC gave 43 mg of the title compound (27%) from 140 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{29}FN_4O_4$: 457, obtained: 457.

Example 6: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1 H-pyrrole-3-carboxylic acid ((S)-3-carbamoyl-3-hydroxy-propyl)-amide



Preparative HPLC gave 15 mg of the title compound (20%) from 81 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{20}H_{21}FN_4O_4$: 401, obtained: 401.

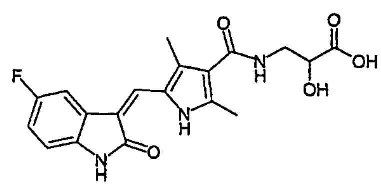
Example 7: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1 H-pyrrole-3-carboxylic acid ((S)-3-hydroxy-4-morpholin-4-yl-4-oxo-butyl)-amide



Preparative HPLC gave 18 mg of the title compound (21%) from 81 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{24}H_{27}FN_4O_5$: 471, obtained: 471.

Examples 8-11: The synthesis of acid (**2-2**) and amides (**2-3**) is shown in Figure 2.

Example 8: 3-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxy-propionic acid

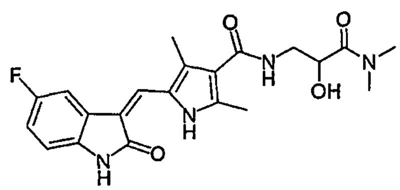


To a solution of compound **1-2** (1.0 mmol) and DIEA (3 equiv) in DMF, the HCl salt of methyl 3-amino-2-hydroxypropionate (1.2 equiv, prepared by refluxing the isoserine in dry methanol with 1.2 equiv HCl) was added. After stirring at 25 °C for 2h (at which time LC-MS showed the completion of the reaction), KOH in water (5 equiv) was added, and the stirring was continued until the hydrolysis was complete (monitored by LC-MS). The solvents were removed by evaporation under reduced pressure. Aqueous HCl (1N) was added to the residue, and the precipitate was collected by filtration, washed

with water, and dried under high vacuum to obtain compound **2-2** (0.33g, 85%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{19}H_{18}FN_3O_5$: 388, obtained: 388.

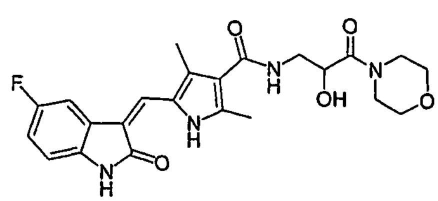
Examples 9-11: The general procedure for the synthesis of amides of **Example 8:** An amine (2 equiv) was added to a solution of the acid, HATU (1.05 mmol), and DIEA (5 equiv) in DMF (5 mL). After the solution was stirred at 25 °C for 2h, aqueous HCl (2 mL, 1N) was added. This solution was subjected to preparative HPLC to obtain the pure amide product, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 9: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-dimethylcarbamoyl-2-hydroxy-ethyl)-amide



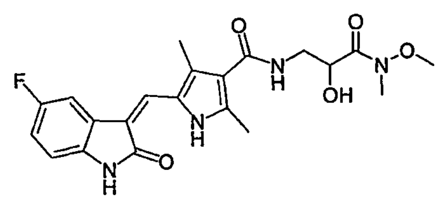
Preparative HPLC gave 50 mg of the title compound (72%) from 65 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{21}H_{23}FN_4O_4$: 415, obtained: 415. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.67 (s, 1H), 10.87 (s, 1H), 7.75 (dd, J = 2.4Hz, 9.6Hz, 1H), 7.70 (s, 1H), 7.56 (t, J = 6.0Hz, 1H), 6.92 (m, 1H), 6.83 (dd, J = 4.8Hz, 8.4Hz, 1H), 4.53 (t, J = 5.6 Hz, 1H), 3.48-3.25 (m, 2H), 3.08 (s, 3H), 2.85 (s, 3H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 10: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-hydroxy-3-(morpholin-4-yl)-3-oxo-propyl)-amide



Preparative HPLC gave 14 mg of the title compound (18%) from 65 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{23}H_{25}FN_4O_5$: 457, obtained: 457. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.68 (s, 1H), 10.90 (s, 1H), 7.75 (dd, J = 2.4Hz, 9.6Hz, 1H), 7.71 (s, 1H), 7.60 (t, J = 6.0Hz, 1H), 6.92 (m, 1H), 6.83 (dd, J = 4.4Hz, 8.4Hz, 1H), 5.2 (b, 1H), 4.51 (t, J = 6.0 Hz, 1H), 3.65-3.35 (m, 10H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 11: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [2-hydroxy-2-(methoxy-methyl-carbamoyl)-ethyl]-amide

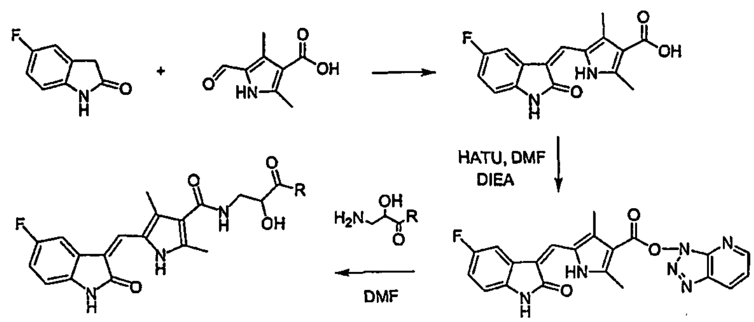


Preparative HPLC gave 16 mg of the title compound (18%) from 80 mg starting material (acid). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{21}H_{23}FN_4O_5$: 431, obtained: 431. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.67 (s, 1H), 10.89 (s, 1H), 7.75 (dd, J = 2.0 Hz, 9.2 Hz, 1H), 7.70 (s, 1H), 7.55 (t, J = 5.6 Hz, 1H), 6.92 (m, 1H), 6.82 (dd, J = 4.8 Hz, 8.8Hz, 1H), 4.51 (t, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.55-3.40 (m, 2H), 3.13 (s, 3H), 2.42 (s, 3H), 2.41 (s, 3H).

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Exemplary Chiral Species

A general scheme for synthesizing chiral species of the invention is outline below:



Scheme 1

Step 1:

A mixture of 5-fluoro-1, 3-dihydroindol-2-one (1.62 g, 10.2 mmol), 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1.96 g, 10.7 mmol), pyrrolidine (12 drops) and absolute ethanol was heated to reflux for 3 hours. The mixture was cooled to 25 °C and the solids were collected by filtration. The solids were stirred with ethanol (30 mL) at 72 °C for 30min. The mixture was cooled to 25 °C and the solids were collected again by filtration, washed with ethanol (6 mL), and dried under vacuum overnight to give an orange solid (Z)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3.094 g, 96%). LC-ESIMS observed $[M+H]^+$ 300.95 (calculated for $C_{16}H_{13}FN_2O_3$ 300.09).

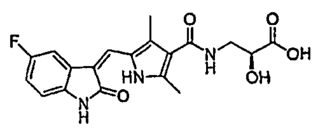
Step 2:

(Z)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3.094 g, 10.3 mmol) was suspended in DMF (15 mL), and stirred for 5 minutes. DIEA (2.7 mL, 15.5 mmol) was then added and the mixture was stirred for 10 minutes. HATU (3.91 g, 10.28 mmol) was added and the reaction mixture was stirred at 25 °C for completion. LC/MS detected the completion of the reaction. Most of the DMF was removed and the residue was suspended in ACN and stirred for another 40 minutes. The solid was collected by filtration, washed with ACN, and dried under high vacuum overnight. (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (3.97 g, 92%) was obtained. LC-ESIMS observed $[M+H]^+$ 418.68 (calculated for $C_{21}H_{15}FN_6O_3$ 418.12).

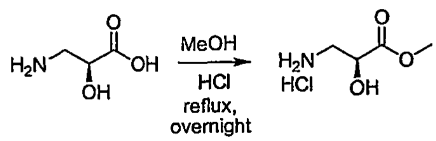
Step 3:

To (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (1.0 eq) DMF solution was added amine (1.2 eq), the reaction mixture was stirred at 25 °C for 2 h. LC/MS was applied to detect the completion of the reaction. Remove DMF under reduced pressure and the crude was precipitated with 5% diethylamine/methanol (3 mL) under sonication, the solid was collected by filtration and washed with 5% diethylamine/methanol (1 mL) twice.

Example 12: Synthesis of (S)-3-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxypropanoic acid

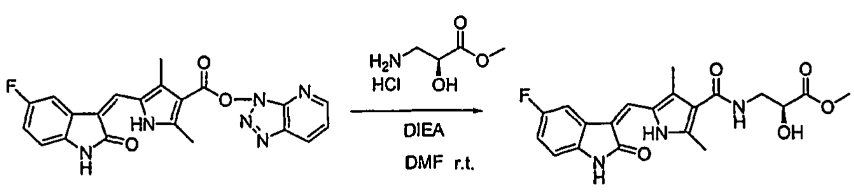


Synthesis of (S)-methyl 3-amino-2-hydroxypropanoate hydrochloride:



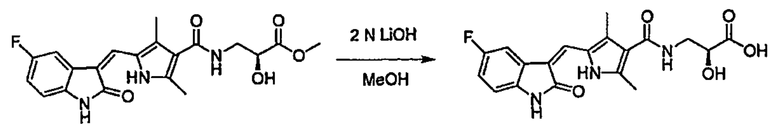
To the (S)-isoserine (921.6 mg, 8.77 mmol) in methanol (20 mL) was added concentrated HCl (0.5 mL), and the mixture was refluxed overnight. The mixture was cooled to 25 °C and the solvent was removed under reduced pressure. The crude material was dried and used directly in the next step.

Synthesis of (S)-3-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxypropanoic acid methyl ester:



To (S)-methyl 3-amino-2-hydroxypropanoate hydrochloride (172.3 mg, 1.11 mmol) DMF solution was added DIEA (0.48 mL, 2.76 mmol) and the mixture was stirred at 25 °C for 20 minutes. (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (174.8 mg, 0.418 mmol) was added, and the mixture was stirred at 25 °C for the completion. The solvent was removed under reduced pressure to afford (S)-3-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxypropanoic acid methyl ester (quantitative yield). The product was used in the next step with no purification. LC-ESIMS observed $[M+H]^+$ 401.98 (calculated for $C_{20}H_{20}FN_3O_5$ 401.15).

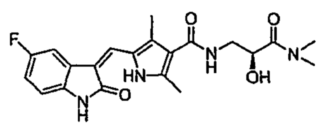
Synthesis of (S)-3-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxypropanoic acid:



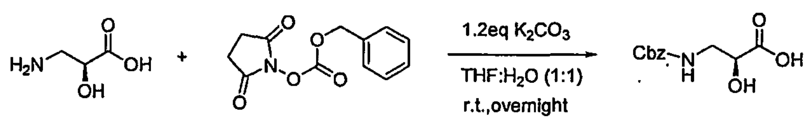
(S)-3-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxypropanoic acid methyl ester (167 mg, 0.418 mmol) and $LiOH \cdot H_2O$ (36 mg, 0.86 mmol) and methanol/water (10 ml/2 mL) was stirred at 25 °C overnight. Most of the solvent was removed under reduced pressure and excess 1N HCl was added to acidify the mixture. The orange solid was collected by filtration and washed with cold methanol to afford (S)-3-({5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-2-hydroxypropanoic acid (yield 88%). LCESIMS observed $[M+H]^+$ 387.96 (calculated for $C_{19}H18FN_3O_5$ 387.12); ^1H NMR (400MHz, DMSO-d_6) δ 13.91 (s, 1H), 10.89 (s, 1H), 7.75 (dd, J = 9.6 Hz, 2.4Hz, 1H), 7.70 (s, 1H), 7.57 (t, J = 6.2Hz, 1H), 6.92 (td, J = 9.2Hz, 2.4Hz, 1H), 6.85-6.82 (m, 1H), 4.17-4.14 (m, 1H), 3.64 (s, 1H), 3.55-3.49 (m, 1H), 3.45-3.39 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H).

Examples 13-17: The general procedure for the synthesis of amides: An amine (1.2 equiv) was added to a suspension of the (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (1.0 eq) in DMF. The mixture was stirred at 25 °C for 2 h and LC/MS was applied to detect the completion of the reaction. The final solution was removed to get the crude solid, which was precipitated in 5% diethylamine/methanol, the solid was collected by filtration and washed with 5% diethylamine/methanol to afford the pure amide product, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 13: Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-dimethylcarbamoyl-2-hydroxy-ethyl)-amide

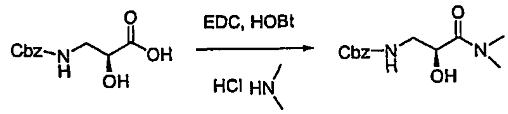


Synthesis of (S)-3-(benzyloxycarbonyl)-2-hydroxypropanoic acid:



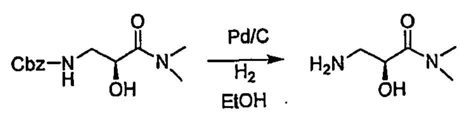
To the THF/water (50 mL/50 mL) solution of (S)-isoserine (2.429 g, 23.12 mmol) was added K_2CO_3 (3.834 g, 27.74 mmol) and *N*-(Benzyloxycarbonyloxy)-succinimide (5.76 g, 23.11 mmol). The reaction mixture was stirred at 25 °C overnight. The reaction mixture was concentrated and diluted with EtOAc and acidified with excess HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with dilute HCl, water, brine and dried over sodium sulfate. The solvent was removed under reduced pressure to afford (S)-3-(benzyloxycarbonyl)-2-hydroxypropanoic acid (5.11 g, 92%), which was used in the next step with no further purification. LC-ESIMS observed $[M+H]^+$ 239.91 (calculated for $C_{11}H_{13}NO_5$ 239.08).

Synthesis of (S)-benzyl 3-(dimethylamino)-2-hydroxy-3-oxopropylcarbamate:



To (S)-3-(benzyloxycarbonyl)-2-hydroxypropanoic acid (377.8 mg, 1.58 mmol) in DMF (5 mL) was added dimethylamine hydrogen chloride (193.2 mg, 2.37 mmol) and DIEA (0.9 mL, 5.17 mmol). The mixture was then stirred for 5 min and EDC (454.3 mg, 2.37 mmol) and HOBt (320.3 mg, 2.37 mmol) were added. The reaction mixture was stirred at 25 °C overnight. DMF was removed under reduced pressure and the crude material was diluted with EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with water, 1N HCl and dried over $NaSO_4$. The solution was concentrated and the crude material was purified by flash chromatography with 0~20% MeOH/DCM to obtain the (S)-benzyl 3-(dimethylamino)-2-hydroxy-3-oxopropylcarbamate (349.2 mg, 83%). LC-ESIMS observed $[M+H]^+$ 266.96 (calculated for $C_{13}H_{18}N_2O_4$ 266.13).

Synthesis of (S)-3-amino-2-hydroxy-*N*,*N*-dimethylpropanamide:

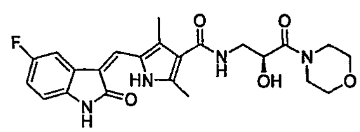


To the degassed (S)-benzyl 3-(dimethylamino)-2-hydroxy-3-oxopropylcarbamate (256.6 mg, 0.964 mmol) in ethanol (10 mL) was added Pd/C (10%, 30 mg) under argon protection, and then the mixture was degassed. The hydrogen balloon was used to provide the H_2 source. The reaction was stirred at 50 °C overnight. The mixture was filtered with Celite 521. The filtrate was evaporated to afford (S)-3-amino-2-hydroxy-*N*,*N*-dimethylpropanamide (125.2 mg, 98%). ^1H NMR (400MHz, $CDCl_3$) δ 4.65 (t, J = 5.4Hz, 1H), 3.71-3.59 (m, 2H), 3.07 (s, 3H), 3.04 (s, 3H), 1.94 (broad s, 2H).

Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-dimethylcarbamoyl-2-hydroxy-ethyl)-amide:

The title compound was obtained following the general procedure for amide synthesis (79%). LC-ESIMS observed $[M+H]^+$ 414.97 (calculated for $C_{21}H_{23}FN_4O_4$ 414.17); ^{1}H NMR (400MHz, DMSO-d_6) δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, J = 9.6 Hz, 2.4Hz, 1H), 7.71 (s, 1H), 7.59 (t, J = 6.2Hz, 1H), 6.92 (td, J = 9.2Hz, 2.4Hz, 1H), 6.85-6.82(m, 1H), 5.04 (d, J = 7.6Hz, 1H), 4.53 (q, J = 6.2Hz, 1H), 3.47-3.41 (m, 1H), 3.36-3.30 (m, 1H), 3.08 (s, 3H), 2.85 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H).

Example 14. Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide



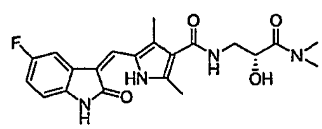
Synthesis of (S)-benzyl 2-hydroxy-3-morpholino-3-oxopropylcarbamate:
Similar method to synthesis of (S)-benzyl 3-(dimethylamino)-2-hydroxy-3-oxopropylcarbamate was applied and the title compound was obtained (yield 86%). LC-ESIMS observed $[M+H]^+$ 408.96 (calculated for $C_{15}H_{20}N_2O_5$ 308.96).

Synthesis of (S)-3-amino-2-hydroxy-1-morpholinopropan-1-one:
Similar method to synthesis of (S)-3-amino-2-hydroxy-*N,N*-dimethylpropanamide was applied and the title compound was obtained (yield 94%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.36-4.34 (m, 1H), 3.75-3.54 (m, 8H), 3.50 (d, J = 4.0Hz, 1H), 2.96-2.79 (m, 2H), 1.94 (broad s, 2H).

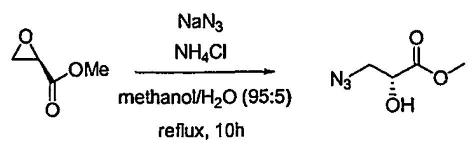
Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide:
The title compound was obtained following the general procedure for amide synthesis (75%). LC-ESIMS observed $[M+H]^+$ 457.01 (calculated for

$C_{23}H_{25}FN_4O_5$ 456.18); ^1H NMR (400MHz, DMSO-d_6) δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, J = 9.6 Hz, 2.4Hz, 1H), 7.71 (s, 1H), 7.59 (t, J = 6.2Hz, 1H), 6.92 (td, J = 9.2Hz, 2.4Hz, 1H), 6.85-6.82(m, 1H), 5.18 (d, J = 8.8Hz, 1H), 4.51 (q, J = 6.0Hz, 1H), 3.61-3.51 (m, 6H), 3.49-3.36 (m, 4H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 15. Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-dimethylcarbamoyl-2-hydroxy-ethyl)-amide

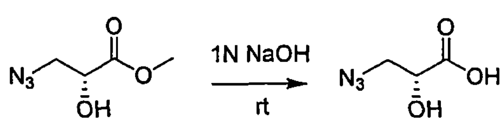


Synthesis of (R)-methyl 3-azido-2-hydroxypropanoate:



Sodium azide (5.487 g, 84.39 mmol) and ammonium chloride (2.257 g, 42.2 mmol) were added to a solution of methyl (2R)-glycidate (2.872 g, 28.13 mmol) in methanol (40 mL) and water (2 mL). After refluxing for 10 h, methanol was evaporated. The mixture was diluted in $CHCl_3$, washed with 1N HCl (5 mL) and extracted. After drying over sodium sulfate, the organic phase was concentrated and purified by flash chromatography to give the (R)-methyl 3-azido-2-hydroxypropanoate (2.82 g, 69%). ^1H NMR (400MHz, $CDCl_3$) δ 4.39-4.36 (m, 1H), 3.84 (s, 3H), 3.67-3.48 (m, 2H), 3.18 (d, J = 4.0Hz, 1H).

Synthesis of (R)-3-azido-2-hydroxypropanoic acid:

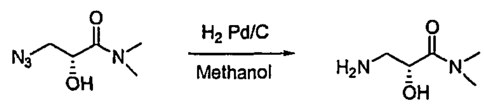


To a solution of (R)-methyl 3-azido-2-hydroxypropanoate (7.3 g, 50.3 mmol) in MeOH (150 mL) at 0 °C was added 1N NaOH (65 mL, 65 mmol). After being stirred at room temperature for 1 h, the mixture was acidified by 1N HCl and extracted with EtOAc. The organic layers were dried over sodium sulfate and

concentrated *in vacuo* to give the acid as a white solid. The compound was used in the next step with no further purification.

Synthesis of (R)-3-azido-2-hydroxy-*N,N*-dimethylpropanamide:
Similar method to synthesis of (S)-benzyl 3-(dimethylamino)-2-hydroxy-3-oxopropylcarbamate was applied and the title compound was obtained (yield 93%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.39-4.36 (m, 1H), 3.67-3.48 (m, 2H), 3.18 (d, J = 4.0Hz, 1H), 3.08 (s, 3H), 3.04 (s, 3H).

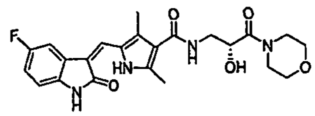
Synthesis of (R)-3-amino-2-hydroxy-*N,N*-dimethylpropanamide:



To the degassed (R)-3-azido-2-hydroxy-*N,N*-dimethylpropanamide (8.37 g, 46.6 mmol) in ethanol (150 mL) was added Pd/C (10%, 837 mg)under argon protection, and then the mixture was degassed. A hydrogen balloon was used to provide an H_2 source. The reaction was stirred at 25 °C for 2 h, and TLC was applied to detect the completion of the reaction. The mixture was filtered with Celite 521. The filtrate was evaporated to afford the desired compound (5.38g, 87%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.65 (t, J = 5.4Hz, 1H), 3.71-3.59 (m, 2H), 3.07 (s, 3H), 3.04 (s, 3H).

Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-dimethylcarbamoyl-2-hydroxy-ethyl)-amide:
The title compound was obtained following the general procedure for amide synthesis (yield 85%), LC-ESIMS observed $[M+H]^+$ 414.97 (calculated for $C_{21}H_{23}FN_4O_4$ 414.17); ^{1}H NMR (400MHz, DMSO-d_6) δ 13.67 (s, 1H), 10.89 (s, 1H), 7.76 (dd, J = 9.6 Hz, 2.4Hz, 1H), 7.71 (s, 1H), 7.59 (t, J = 6.2Hz, 1H), 6.92 (td, J = 9.2Hz, 2.4Hz, 1H), 6.85-6.82 (m, 1H), 5.04 (d, J = 7.6Hz, 1H), 4.53 (q, J = 6.2Hz, 1H), 3.47-3.41 (m, 1H), 3.36-3.30 (m, 1H), 3.08 (s, 3H), 2.85 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H).

Example 16. Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide

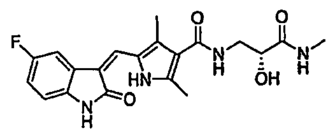


Synthesis of (R)-3-azido-2-hydroxy-1-morpholinopropan-1-one:
Similar method to synthesis of (S)-benzyl 3-(dimethylamino)-2-hydroxy-3-oxopropylcarbamate was applied and the title compound was obtained (yield 90%), ^{1}H NMR (400MHz, $CDCl_3$) δ 4.55 (t, J = 5.2Hz, 1H), 3.71-3.60 (m, 6H), 3.48-3.41 (m, 3H), 3.40-3.35 (m, 2H).

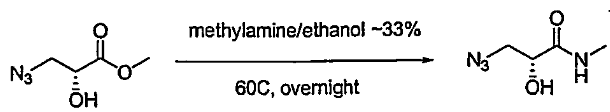
Synthesis of (R)-3-amino-2-hydroxy-1-morpholinopropan-1-one:
A similar method to synthesis of (R)-3-amino-2-hydroxy-*N,N*-dimethylpropanamide was used and the title compound was obtained in high yield (yield 95%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.36-4.34 (m, 1H), 3.75-3.54 (m, 8H), 3.50 (d, J = 4.0Hz, 1H), 2.96-2.79 (m, 2H), 1.94 (broad s, 2H).

Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-hydroxy-3-morpholin-4-yl-3-oxo-propyl)-amide:
The title compound was obtained following the general procedure for amide synthesis (yield 75%). LC-ESIMS observed $[M+H]^+$ 457.01 (calculated for $C_{23}H_{25}FN_4O_5$ 456.18); ^{1}H NMR (400MHz, DMSO-d_6) δ 13.68 (s, 1H), 10.89 (s, 1H), 7.76 (dd, J = 9.6 Hz, 2.4Hz, 1H), 7.71 (s, 1H), 7.59 (t, J = 6.2Hz, 1H), 6.92 (td, J = 9.2Hz, 2.4Hz, 1H), 6.85-6.82 (m, 1H), 5.18 (d, J = 6.4Hz, 1H), 4.54-4.49 (m, 1H), 3.61-3.51 (m, 6H), 3.49-3.36 (m, 4H), 2.43 (s, 3H), 2.41 (s, 3H).

Example 17. Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-hydroxy-2-methylcarbamoyl-ethyl)-amide



Synthesis of (R)-3-azido-2-hydroxy-*N*-methylpropanamide:



(R)-methyl 3-azido-2-hydroxypropanoate (505.4 mg, 3.48 mmol) and methylamine ethanol solution (15 mL) was sealed and stirred at 60 °C oil bath overnight. TLC analysis was applied to detect the reaction completion. The solvent was removed and the crude was purified by flash chromatography (0~20% Methanol/DCM) to afford (R)-3-azido-2-hydroxy-*N*-methylpropanamide (385.2 mg, yield 77%), ^{1}H NMR (400MHz, $CDCl_3$) δ 6.90-6.70 (broad s, 1H), 4.28-4.24 (m, 1H), 3.69-3.57 (m, 3H), 2.87 (d, J = 5.6Hz, 3H).

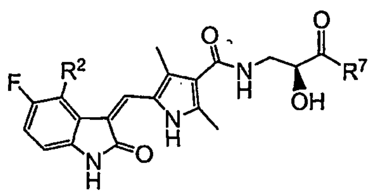
Synthesis of (R)-3-amino-2-hydroxy-N-methylpropanamide:

Similar method to synthesis of (R)-3-amino-2-hydroxy-*N*,*N*-dimethylpropanamide was used and the title compound was obtained (yield 98%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.05 (broad s, 1H), 3.97 (t, J = 5.6Hz, 1H), 3.12-2.96 (m, 2H), 2.85 (d, J = 5.2Hz, 3H), 1.90 (broad, 2H).

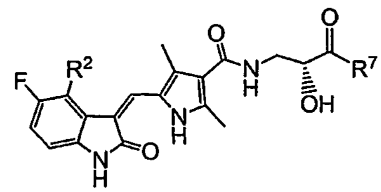
Synthesis of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-hydroxy-2-methylcarbamoyl-ethyl)-amide:

The title compound was obtained following the general procedure for amide synthesis (yield 86%), LC-ESIMS observed $[M+H]^+$ 400.96 (calculated for $C_{20}H_{21}FN_4O_4$ 400.15); ^{1}H NMR (400MHz, DMSO-d_6) δ 13.69 (s, 1H), 10.89 (s, 1H), 7.87 (d, J = 4.8Hz, 1H), 7.76 (dd, J = 9.6 Hz, 2.4Hz, 1H), 7.71 (s, 1H), 7.52 (t, J = 5.6Hz, 1H), 6.95-6.90 (m, 1H), 6.85-6.82 (m, 1H), 5.83 (d, J = 5.2Hz, 1H), 4.07-4.03 (m, 1H), 3.57-3.51 (m, 1H), 3.37-3.30 (m, 1H), 2.62 (d, J = 4.4Hz, 3H) 2.45 (s, 3H), 2.42 (s, 3H).

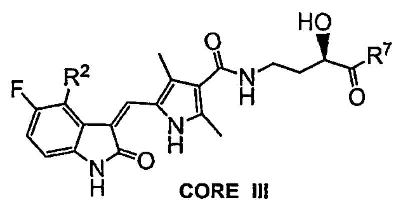
Examples 18 – 217: Still further amide examples are shown in the following table:



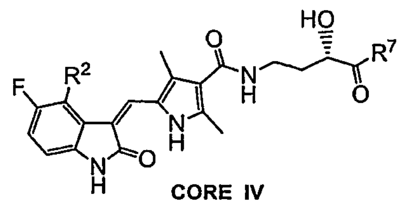
CORE I



CORE II



CORE III



CORE IV

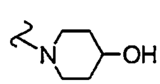
In the above core structures, R^2 is selected from the group consisting of hydrogen and fluoro; and R^7 is selected from the group consisting of hydroxyl or radicals represented by the following structures:

Ex#	Core	R^7	Ex#	Core	R^7	Ex#	Core	R^7
18	I	a	68	II	a	118	III	a
19	I	b	69	II	b	119	III	b
20	I	c	70	II	c	120	III	c
21	I	d	71	II	d	121	III	d
22	I	e	72	II	e	122	III	e
23	I	f	73	II	f	123	III	f
24	I	g	74	II	g	124	III	g
25	I	h	75	II	h	125	III	h
26	I	i	76	II	i	126	III	i
27	I	j	77	II	j	127	III	j
28	I	k	78	II	k	128	III	k
29	I	l	79	II	l	129	III	l
30	I	m	80	II	m	130	III	m
31	I	n	81	II	n	131	III	n
32	I	o	82	II	o	132	III	o

Ex#	Core	R^7	Ex#	Core	R^7	Ex#	Core	R^7
33	I	p	83	II	p	133	III	p
34	I	q	84	II	q	134	III	q
35	I	r	85	II	r	135	III	r
36	I	s	86	II	s	136	III	s
37	I	t	87	II	t	137	III	t
38	I	u	88	II	u	138	III	u
39	I	v	89	II	v	139	III	v
40	I	w	90	II	w	140	III	w
41	I	x	91	II	x	141	III	x
42	I	y	92	II	y	142	III	y
43	I	z	93	II	z	143	III	z
44	I	aa	94	II	aa	144	III	aa
45	I	ab	95	II	ab	145	III	ab
46	I	ac	96	II	ac	146	III	ac
47	I	ad	97	II	ad	147	III	ad
48	I	ae	98	II	ae	148	III	ae
49	I	af	99	II	af	149	III	af
50	I	ag	90	II	ag	150	III	ag
51	I	ah	100	II	ah	151	III	ah
52	I	ai	102	II	ai	152	III	ai
53	I	aj	103	II	aj	153	III	aj
54	I	ak	104	II	ak	154	III	ak
55	I	al	105	II	al	155	III	al
56	I	am	106	II	am	156	III	am
57	I	an	107	II	an	157	III	an
58	I	ao	108	II	ao	158	III	ao
59	I	ap	109	II	ap	159	III	ap
60	I	aq	110	II	aq	160	III	aq
61	I	ar	111	II	ar	161	III	ar
62	I	as	112	II	as	162	III	as
63	I	at	113	II	at	163	III	at
64	I	au	114	II	au	164	III	au
65	I	av	115	II	av	165	III	av
66	I	aw	116	II	aw	166	III	aw
67	I	ax	117	II	ax	167	III	ax

Ex#	Core	R^7	Ex#	Core	R^7
168	IV	a	194	V	aa
169	IV	b	195	V	ab
170	IV	c	196	V	ac
171	IV	d	197	V	ad
172	IV	e	198	V	ae
173	IV	f	199	V	af
174	IV	g	200	V	ag
175	IV	h	201	V	ah
176	IV	i	202	V	ai
177	IV	j	203	V	aj
178	IV	k	204	V	ak
179	IV	l	205	V	al
180	IV	m	206	V	am
181	IV	n	207	V	an
182	IV	o	208	V	ao
183	IV	p	209	V	ap
184	IV	q	210	V	aq
185	IV	r	211	V	ar
186	IV	s	212	V	as
187	IV	t	213	V	at
188	IV	u	214	V	au
189	IV	v	215	V	av
190	IV	w	216	V	aw
191	IV	x	217	V	ax
192	IV	y			
193	IV	z			

In the above table, R^7 is selected from the following radicals: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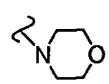
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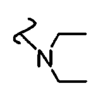
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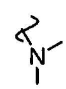
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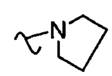
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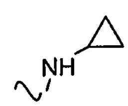
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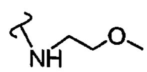
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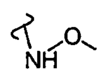
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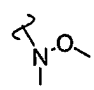
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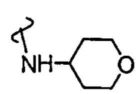
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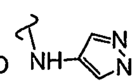
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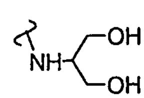
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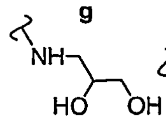
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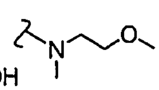
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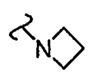
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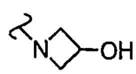
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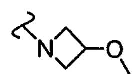
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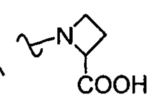
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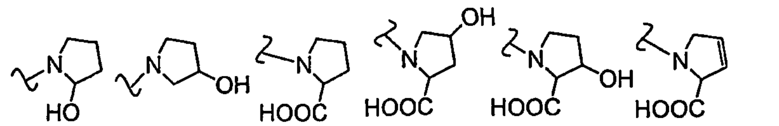
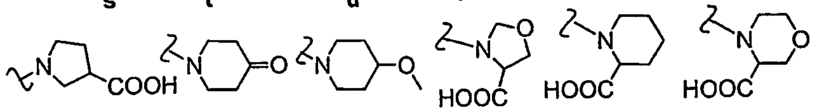
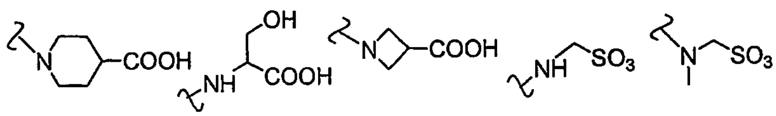


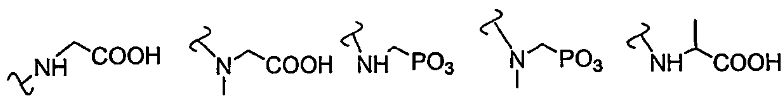
s t u v w x



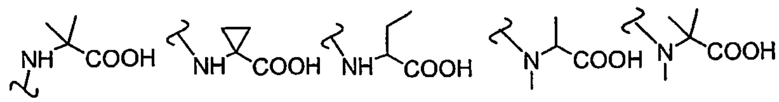
y z aa ab ac ad



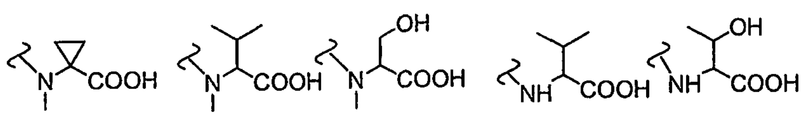
ae af ag ah ai



aj ak al am an



ao ap aq ar as



at au av aw ax

These amide examples **18-217** can be made by those skilled in the art following the above procedure and/or known procedures.

VEGFR Biochemical Assay

The compounds were assayed for biochemical activity by Upstate Ltd at Dundee, United Kingdom, according to the following procedure. In a final reaction volume of 25 μl, KDR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.33 mg/ml myelin basic protein, 10 mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as

required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μl of a 3% phosphoric acid solution. 10 μl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

<u>Cellular Assay</u>: HUVEC: VEGF induced proliferation

The compounds were assayed for cellular activity in the VEGF induced proliferation of HUVEC cells. HUVEC cells (Cambrex, CC-2517) were maintained in EGM (Cambrex, CC-3124) at 37°C and 5% CO_2. HUVEC cells were plated at a density 5000 cells/well (96 well plate) in EGM. Following cell attachment (1hour) the EGM-medium was replaced by EBM (Cambrex, CC-3129) + 0.1% FBS (ATTC , 30-2020) and the cells were incubated for 20 hours at 37°C. The medium was replaced by EBM +1% FBS, the compounds were serial diluted in DMSO and added to the cells to a final concentration of 0 – 5,000 nM and 1% DMSO. Following a 1 hour pre-incubation at 37°C cells were stimulated with 10ng/ml VEGF (Sigma, V7259) and incubated for 45 hours at 37°C. Cell proliferation was measured by BrdU DNA incorporation for 4 hours and BrdU label was quantitated by ELISA (Roche kit, 16472229) using 1M H_2SO_4 to stop the reaction. Absorbance was measured at 450nm using a reference wavelength at 690nm.

<u>Detailed Description of Figures</u>:

Figure 1 is a scheme showing the synthesis of the acid **1-3** and the corresponding amides, **1-4**. The starting carboxylic acid is synthesized according to the supplemental material of Sun, L.; et al., *J. Med. Chem.* **2003**, *46*, 1116-1119. The intermediate, **1-2**, is formed by reaction of the acid with HATU in the presence of 3 equivalents of Hunig's base, or di-isopropyl ethylamine (DIEA). A solid precipitated after 15 minutes and the solid was

isolated and characterized. This was then reacted with 1.5 equivalents of methyl (2S)-4-amino-2-hydroxybutyrate in DMF and 3 equivalents of Hunig's base. The methyl ester was hydrolyzed with 5 equivalents of KOH in water. Acidifying the reaction mixture enabled the isolation of the free acid, **1-3**. This acid was then reacted with HATU in the presence of 3 equivalents of DIEA in DMF. An amine (2 equivalents) was added and after reacting for 2 hours, the amide was isolated by preparative HPLC.

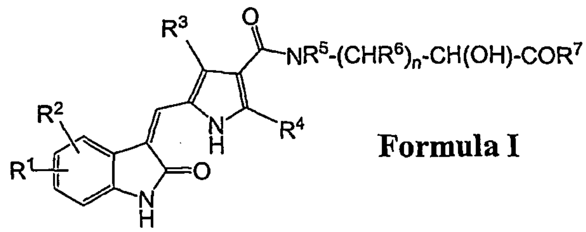
Figure 2 is a scheme showing the synthesis of the amide series, **2-3**. The activated acid, **1-2** is reacted with methyl 3-amino-2-hydroxypropionate hydrochloride in the presence of 3 equivalents of base (DIEA) in DMF. After stirring for 2 h at room temperature, KOH, 5 equivalents, in water was added and stirring continued until ester hydrolysis was complete. The acid was isolated after acidification of the reaction mixture. The free acid was then added to HATU (1.05 equivalent), DIEA (5 equivalents), and an amine (2 equivalents) in DMF. The mixture was stirred for 2 h at room temperature and the mixture was acidified. The pure product was isolated by preparative HPLC.

Figure 3 shows example compounds and some of their activities against KDR. The units of IC_{50} is in μM.

Figure 4 shows additional compounds that were tested for activity.

What is claimed is:

1. A compound represented by Formula (I):



Formula I

wherein:

R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl;

R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, (C2-C8) alkoxyalkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino;

R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide;

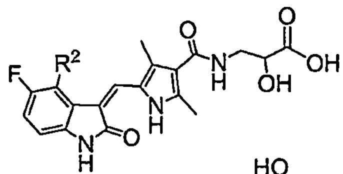
R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen and (C1-C6) alkyl;

R^7 is selected from the group consisting of hydroxy, (C1-C6) O-alkyl, (C3-C8) O-cycloalkyl, and NR^8R^9; where R^8 and R^9 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^8 and R^9 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; and

n is 1, 2, or 3;

or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

2. The compound, salt, tautomer, or prodrug according to claim 1 selected from the group represented by the following structures: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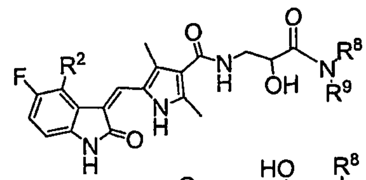
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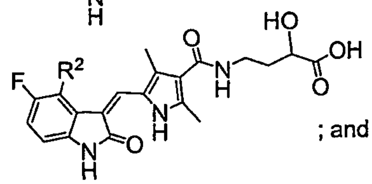
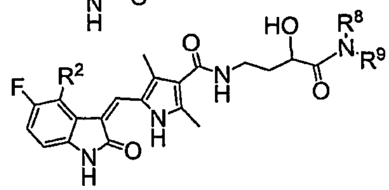
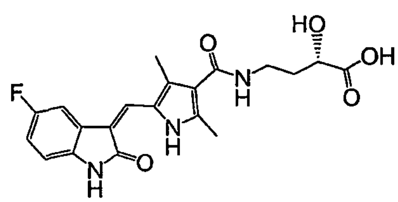

; and


wherein R^2 is selected from the group consisting of hydrogen and fluoro.

3. The compound, salt, tautomer, or prodrug according to claim 1 represented by the following structure: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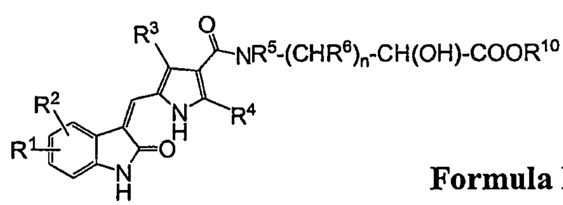
4. The compound, salt, tautomer, or prodrug according to claim 1 represented by Formula **(II)**:



Formula II

wherein R^{10} is selected from the group consisting of hydrogen, (C1-C6) alkyl, and (C3-C8) cycloalkyl.

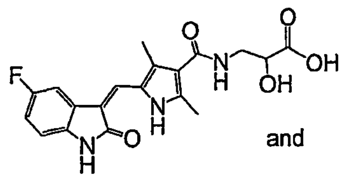
5. The compound, salt, tautomer, or prodrug according to claim 4, wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen and fluoro;

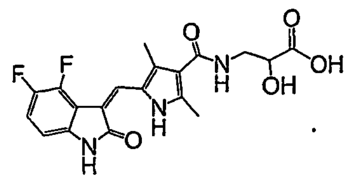
R^3 and R^4 are methyl;

R^5, R^6, and R^{10} are hydrogen; and **n** is 1 or 2.

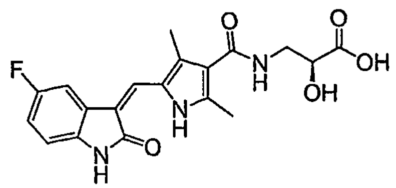
6. The compound, salt, tautomer, or prodrug according to claim 5 selected from the group consisting of:



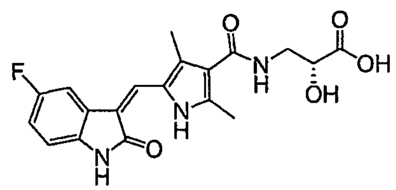
and



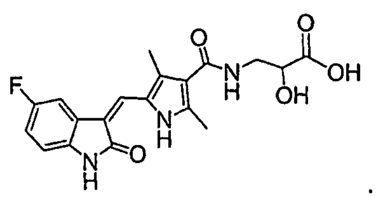
7. The compound, salt, tautomer, or prodrug according to claim 5 represented by the following structure:



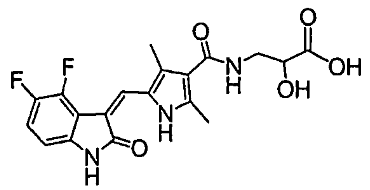
8. The compound, salt, tautomer, or prodrug represented by the following structure:



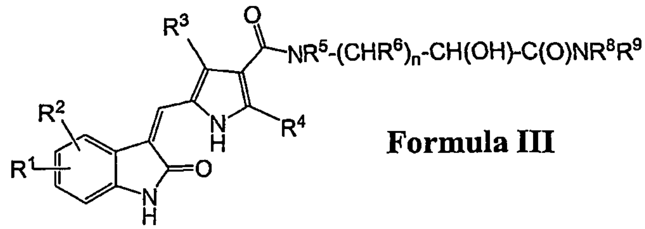
9. The compound, salt, tautomer, or prodrug according to claim 6 represented by the following structure:



10. The compound, salt, tautomer, or prodrug according to claim 6 represented by the following structure:



11. A compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (**III**):



Formula III

12. The compound, salt, tautomer, or prodrug of claim 11, wherein:

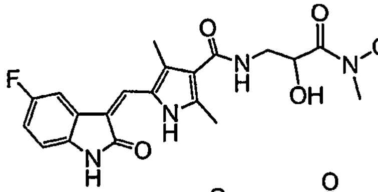
R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, cyano;

R^3, R^4, R^5 and R^6 are independently hydrogen or (C1-C6))alkyl;

n is 1 or 2; and

R^8 and R^9 are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^8 and R^9 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids.

13. The compound, salt, tautomer, or prodrug according to claim 12 selected from the group represented by the following structures: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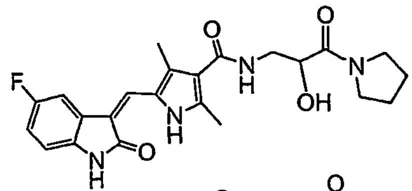
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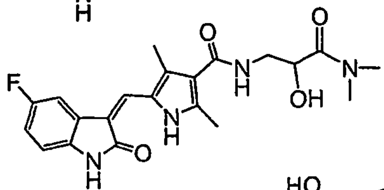
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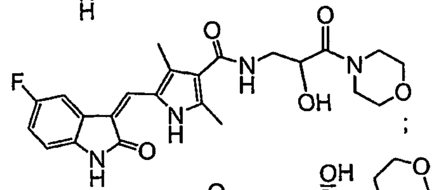
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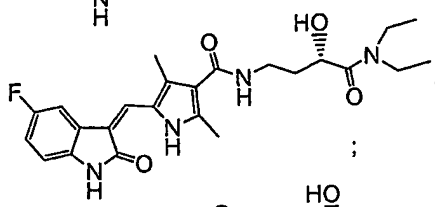
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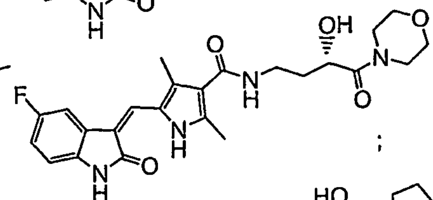
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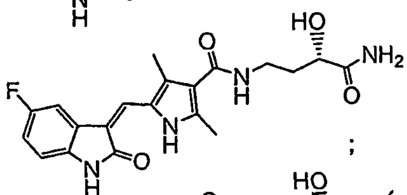
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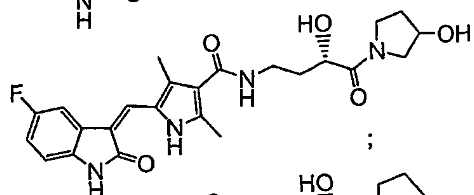
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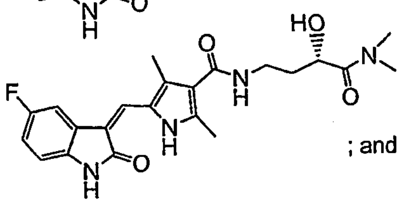
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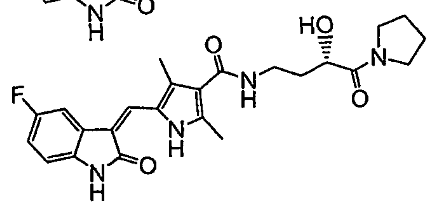
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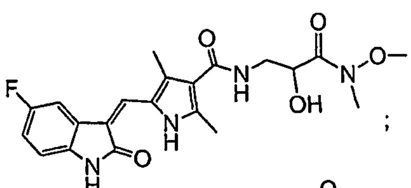
14. The compound, salt, tautomer, or prodrug according to claim 12 wherein **n** is 1.

15. The compound, salt, tautomer, or prodrug according to claim 13 represented by the following structures: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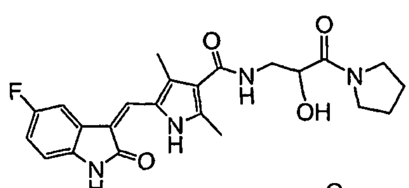
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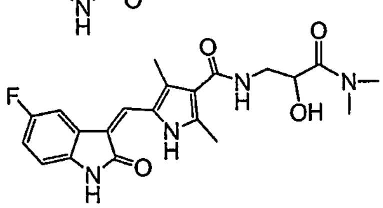
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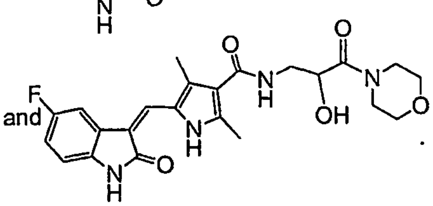
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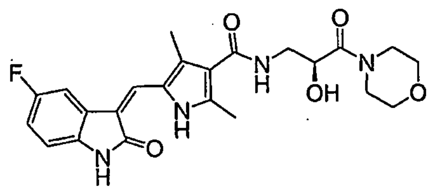
16. The compound, salt, tautomer, or prodrug according to claim 14 selected from the group represented by the following structures: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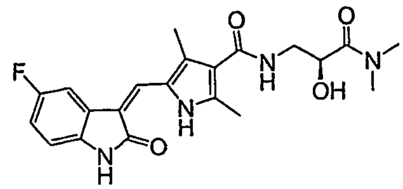
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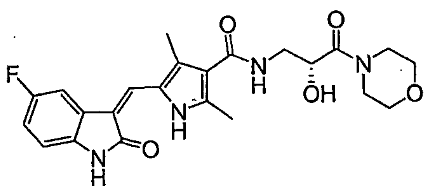
17. The compound, salt, tautomer, or prodrug according to claim 14 selected from the group represented by the following structures: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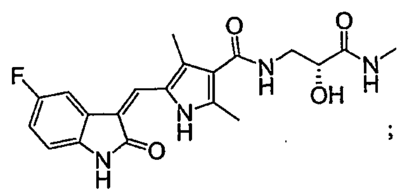
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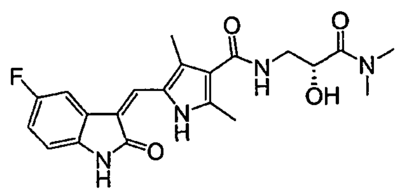
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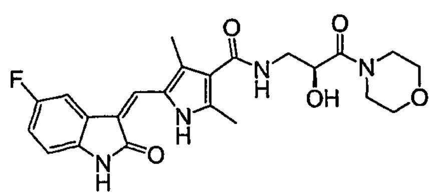
18. The compound, salt, tautomer, or prodrug represented by the following structure: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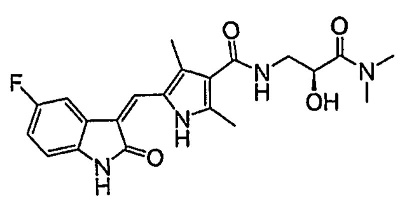
19. The compound, salt, tautomer, or prodrug represented by the following structure: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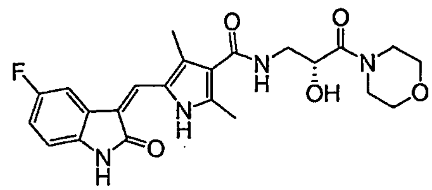
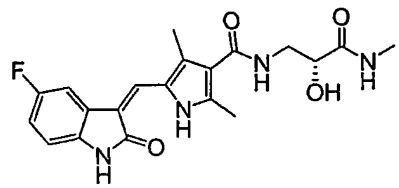
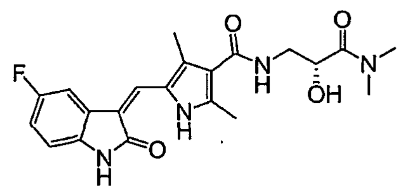
20. The compound, salt, tautomer, or prodrug represented by the following structure:



21. The compound, salt, tautomer, or prodrug according to claim 14 selected from the group represented by the following structures:

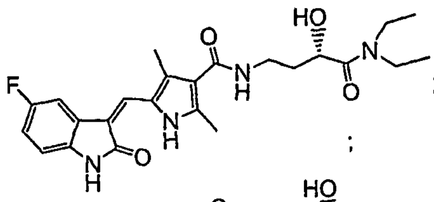


22. The compound, salt, tautomer, or prodrug according to claim 14 selected from the group represented by the following structures:



23. The compound, salt, tautomer, or prodrug according to claim 12 wherein **n** is 2.

24. The compound, salt, tautomer, or prodrug according to claim 23 represented by the following structures:



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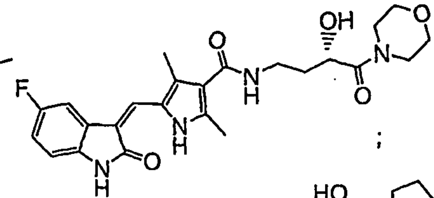

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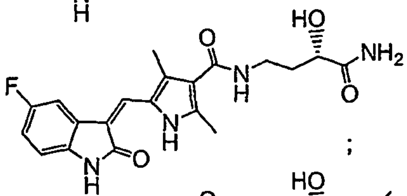

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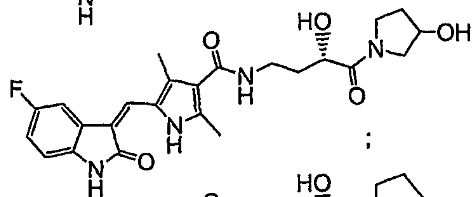

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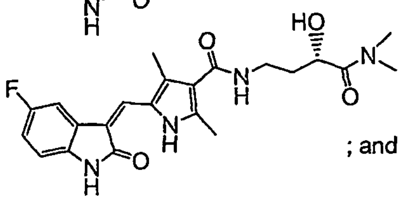

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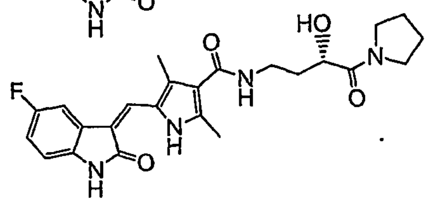
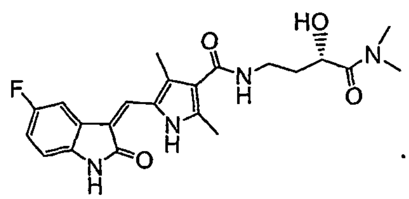


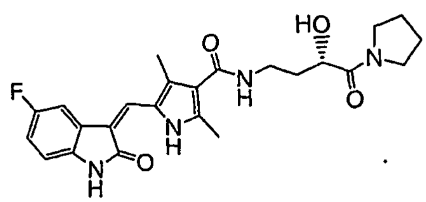
.

25. The compound, salt, tautomer, or prodrug according to claim 23 represented by the following structure:



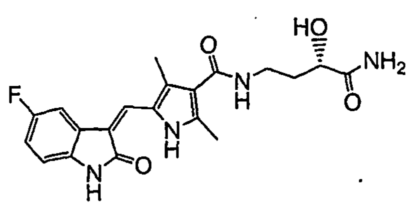
.

26. The compound, salt, tautomer, or prodrug according to claim 23 represented by the following structure:



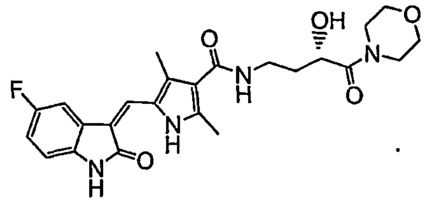
.

27. The compound, salt, tautomer, or prodrug according to claim 23 represented by the following structure:

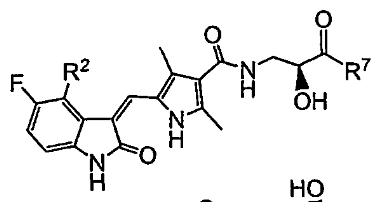
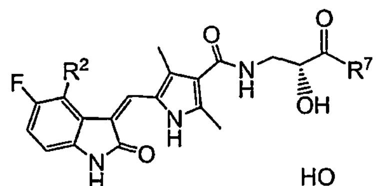
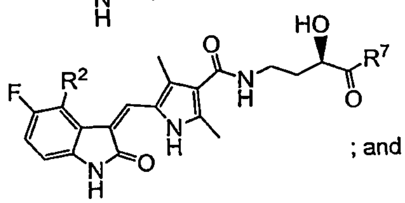
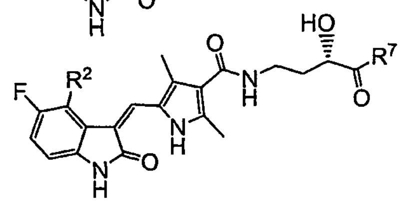


.

28. The compound, salt, tautomer, or prodrug according to claim 23 represented by the following structure:



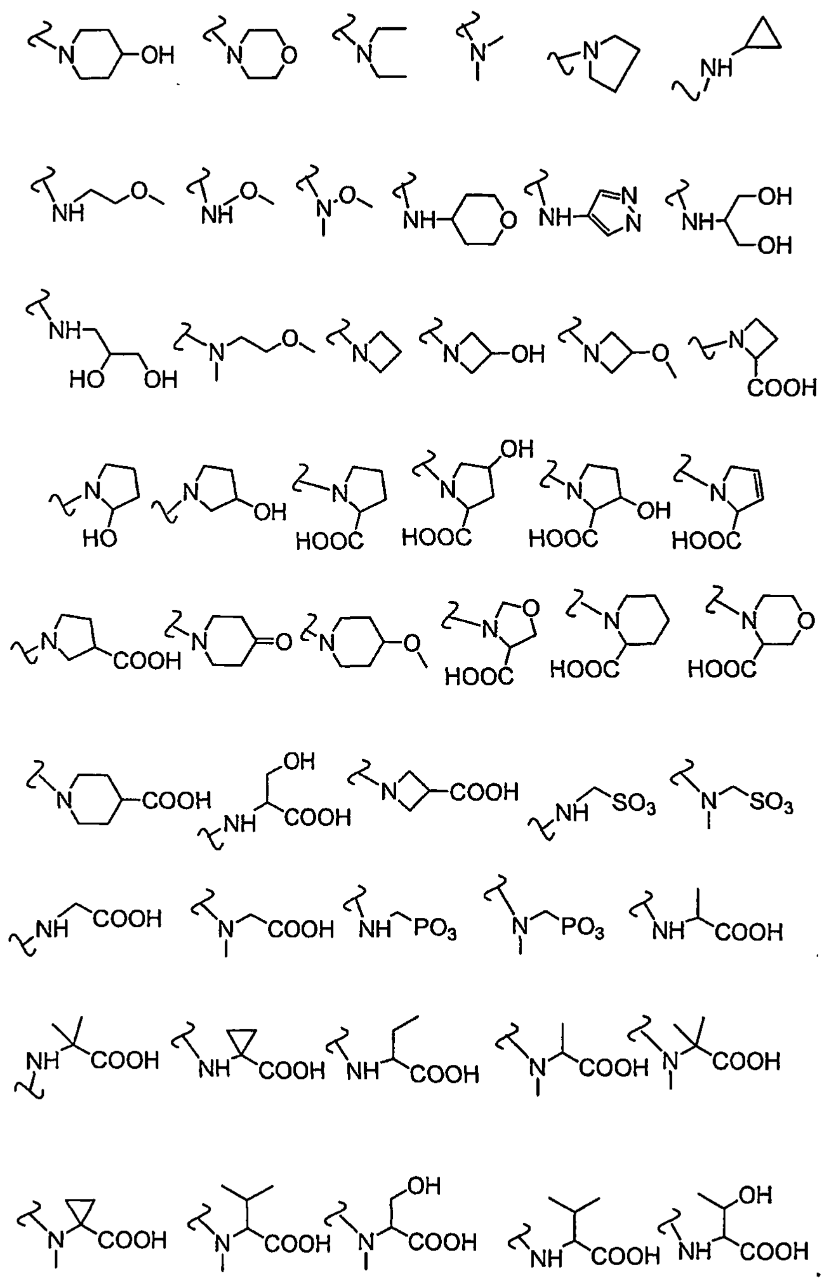
29. The compound, salt, tautomer, or prodrug according to claim 1 selected from the group represented by the following structures:


;

;

; and


wherein:

R^2 is selected from the group consisting of hydrogen and fluoro; and

R^7 is selected from the group consisting of hydroxyl or radicals represented by the following structures:

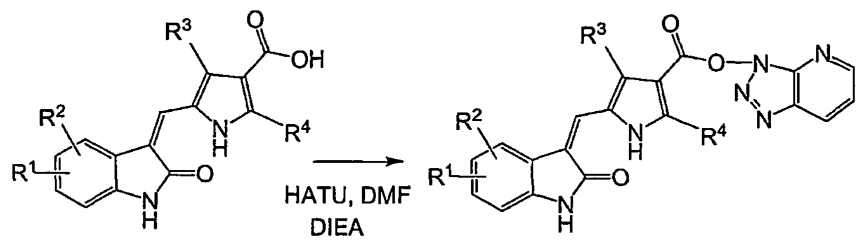


30. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1-29.

31. The method of claim 30, wherein said protein kinase is selected from the group of receptors consisting of VEGF, PDGF, c-kit, Flt-3, Axl, and TrkA.

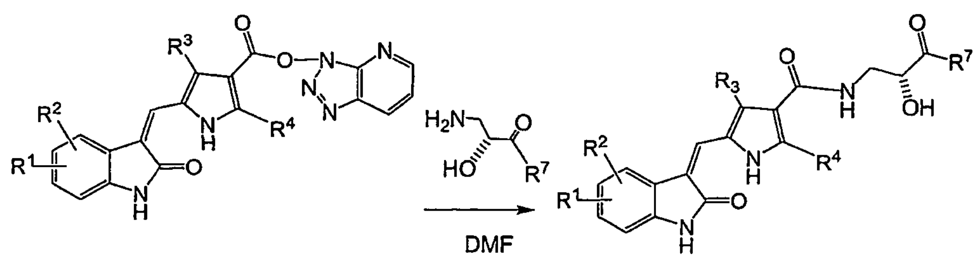
32. A process for synthesizing a pyrrolyl-indolinone having a chiral hydroxyl, the process comprising the following steps:

Step A: Converting a first intermediate to a second intermediate according to the following reaction:



; and then

Step B: Converting the second intermediate to the pyrrolyl-indolinone according to the following reaction:



wherein:

R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, protected amino, protected (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl;

R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, (C2-C8) alkoxyalkyl, protected amino, protected (C1-C6) alkylamino, (C6-C10) arylamino;

R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C6-C10) aryl, (C5-C10) heteroaryl, and amide;

R^4 is selected from the group consisting of hydrogen and (C1-C6) alkyl; and

R^7 is selected from the group consisting of hydroxy, (C1-C6) O-alkyl, (C3-C8) O-cycloalkyl, and NR^8R^9; where R^8 and R^9 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphonic acid, (C1-C6) alkyl sulfonic acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C8) aryl, (C5-C8) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^8 and R^9 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids.

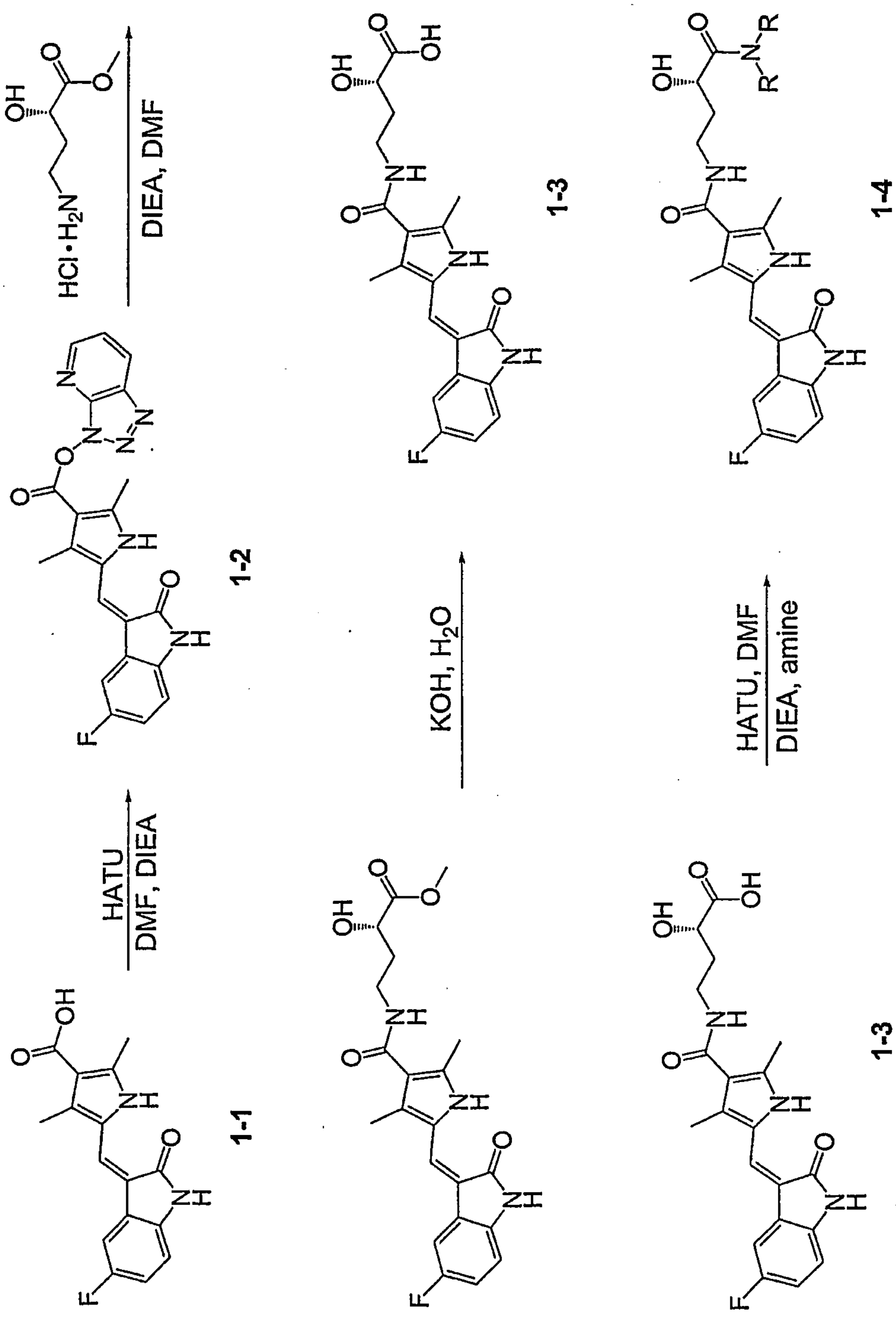

HATU
DMF, DIEA
1-1
1-2
HCl • H2N
DIEA, DMF
KOH, H2O
1-3
HATU, DMF
DIEA, amine
1-4

Figure 1

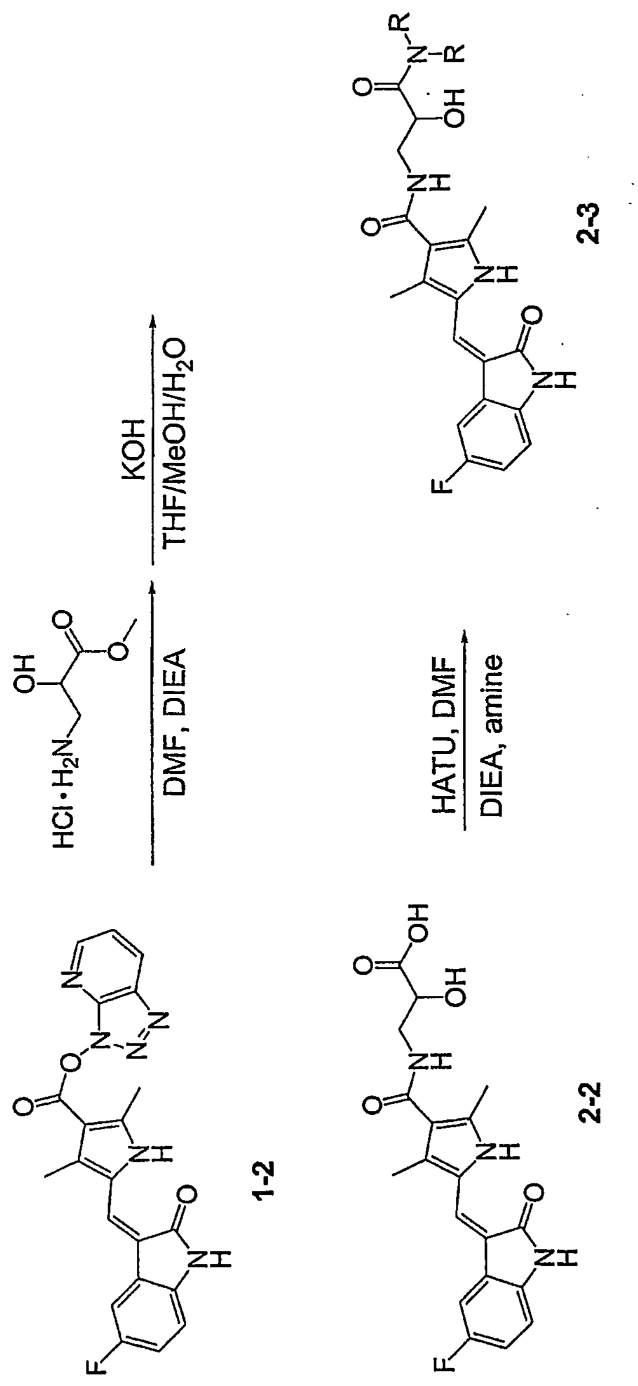

HCl • H2N OH O
DMF, DIEA
KOH
THF/MeOH/H2O
HATU, DMF
DIEA, amine
1-2
2-2
2-3

Figure 2

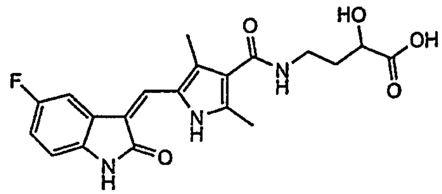
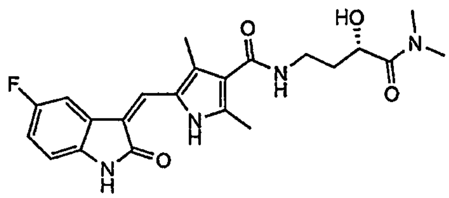
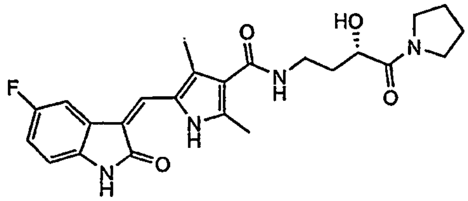
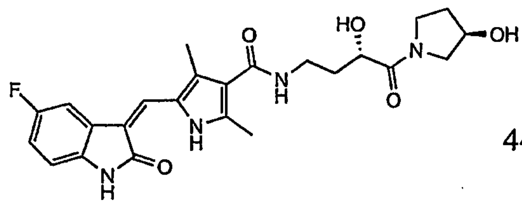
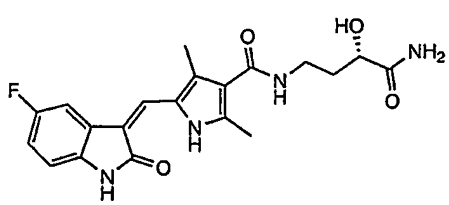
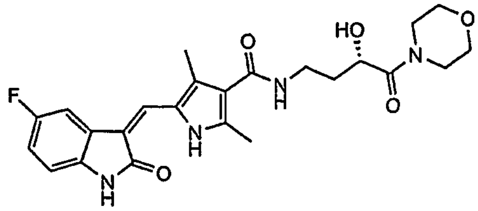
		M.W.	IC_{50} (μM)
1002		414.4	--
Ex. 304		456.5	<0.003
Ex. 302		456.5	<0.003
Ex. 303		440.5	0.01
Ex. 306		430.4	<0.003
Ex. 307		430.4	0.003

Figure 3

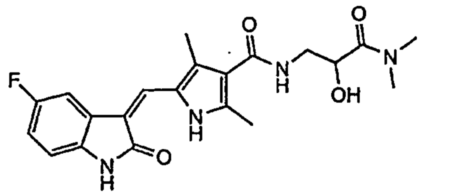
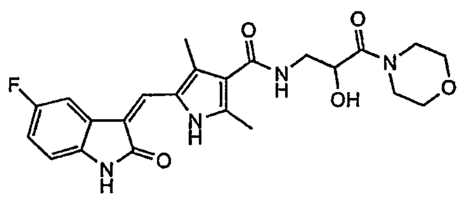
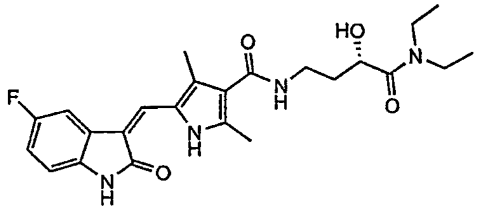
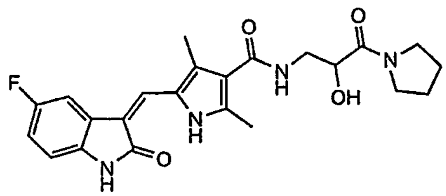
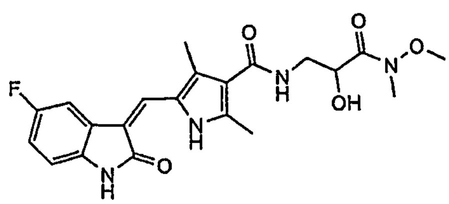
		M.W.	KDR
Ex. 309		414.4	--
Ex. 310		456.5	--
Ex. 305		456.5	--
1001		440.5	--
Ex. 311		430.4	--

Figure 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/20363

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/4015(2006.01);C07D 209/10(2006.01)

USPC: 514/415;548/468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/415; 548/468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST/WEST, STN Structure Search, Registry, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/053686 (Liang) 16 June 2005 (16.06.2005), the whole document.	1-32
A	WO 03/070725 (Jin et al) 28 August 2003 (28.08.2003), the whole document.	1-29 and 32

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
23 August 2006 (23.08.2006)

Date of mailing of the international search report
12 OCT 2006

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Form PCT/ISA/210 (second sheet) (April 2005)